Seminars in Arthritis and Rheumatism 51 (2021) 627–639

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Structural damage in rheumatoid arthritis assessed by musculoskeletal ultrasound: A systematic literature review by the Structural Joint Damage Task Force of the OMERACT Ultrasound Working Group

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ARTICLE INFO

Keywords:
Systematic literature review
Rheumatoid arthritis
Ultrasound
OMERACT
Bone erosion
Cartilage damage

ABSTRACT

Objectives: To identify and synthesize the evidence for the use and measurement properties of musculoskeletal ultrasound in assessing structural joint damage in patients with rheumatoid arthritis (RA).
Methods: A systematic literature search (SLR) of the PubMed, Embase and Cochrane Library was performed. Original articles were included published in English reporting on ultrasound of bone erosion, cartilage damage and the measurement properties of ultrasound according to the OMERACT filter 2.1.
Results: Of the 1.495 identified articles 149 were included in the final review, most of which reported on cross-sectional studies and used the OMERACT definitions for ultrasonographic pathology. Among these, bone erosions were assessed in 139 (93.3%), cartilage damage in 24 (16.1%), enthesophytes in 8 (5.4%), osteophytes in 15 (10.1%) and malalignment and ankylosis in a single (0.9%) study, respectively. Most studies (126/149, 84.6%) assessed the joints of the hands. The overwhelming majority of studies (127/149, 85.2%) assessed structural joint damage bilaterally. Validity, reliability and responsiveness were assessed in 21 (14.1%), 34 (22.8%) and 17 (11.4%) studies, respectively.
Conclusion: While the results of this SLR suggest that ultrasound is a sensitive, reliable and feasible tool to detect damage in RA, they also highlight the need for further research and validation. Findings of this SLR will inform the next steps of the OMERACT Ultrasound Working Group in developing an ultrasound score for assessing structural joint damage in patients with RA.

Introduction

Early diagnosis is the key to a successful therapy in rheumatoid arthritis (RA) and to prevent the progression of structural damage in synovial joints [1]. Joint damage in RA includes, among others loss of hyaline cartilage [2] and bone erosions [3]. The detection of these two components is crucial not only for diagnosis but also for monitoring of therapeutic targets [4]. Malalignment can also be observed in RA, which however is less commonly used as an outcome parameter [5,6]. The occurrence of osteophytes is mainly regarded as a sign of secondary osteoarthritis [7,8] while some suggest a more direct association with RA disease [9].

Conventional radiography (CR) is the most commonly used imaging technique to identify patients with structural joint damage in daily clinical practice and research. Radiographic scores to quantify damage assessed are published, validated and broadly used, particularly in clinical trials [10,11]. Over the last two decades, several other imaging techniques like musculoskeletal ultrasound, magnetic resonance imaging (MRI) and computed

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https://doi.org/10.1016/j.semarthrit.2021.02.010

tomography (CT) have been reported as sensitive and reliable alternatives to detect both cartilage damage [2,12] and bone erosions [3,13].

Musculoskeletal ultrasound has several advantages over MRI, CT and CR. Ultrasound is easily and immediately available, relatively cheap, not associated with radiation, and can be applied to almost all synovial joints within the framework of a single examination and to all patients. Joints can be additionally examined for the presence of erosions, cartilage loss but also synovitis and in addition to articular structures, the involvement of periarticular tissues such as tendon damage, tenosynovitis or enthesitis.

Several sonographic scoring systems for erosions and/ or cartilage damage have been proposed over the last few decades, none of which are utilized widely [14–18]. A semiquantitative scoring system for cartilage damage detected by ultrasound was developed recently by the Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group and was shown to be reliable in the assessment of hyaline cartilage of the metacarpal head [2].

We therefore aimed to systematically review current evidence for the use of ultrasound in detecting structural joint damage in patients with RA. We furthermore aimed to gain an understanding of the definitions and scoring systems which are reported in published literature and to evaluate their metric properties according to the OMERACT filter 2.1, including recommendations for target joints.

Methods

Search strategy

Members of the Structural Joint Damage Task Force of the OMERACT Ultrasound WG used the “Population, Intervention, Control and Outcome” (PICO) system to develop the search strategy (Supplementary File) [19]. Subsequently, a systematic literature search with the key words rheumatoid arthritis, ultrasound, bones/cartilage/joints and damage (for exact search terms see Supplementary File) was performed in the Embase, Medline and Cochrane Central Register of Controlled Trials databases. Original articles published until October 2020 and abstracts presented at the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) annual scientific meetings from January 2018 to October 2020 assessing joint damage in RA by ultrasound were screened. To ensure not missing any suitable articles, an additional hand search was performed in Scopus. Titles, abstracts and full reports of articles were screened for inclusion and exclusion criteria. We included a) original articles or abstracts presented at EULAR or ACR scientific meeting; b) written in English; c) in which the study population included adult ($\geq$18 years) patients with RA or suspected RA and which d) assessed damage by ultrasound. Studies were excluded if they featured less than 20 included patients with RA/suspected RA.

Data extraction

We used a standardized template adapted from previous systematic literature reviews (SLRs) performed by the OMERACT Ultrasound WG [20]. Data from selected articles regarding study population, imaging techniques, number of included patients, joints and lesions assessed, scoring system and main findings regarding the study question were extracted.

Assessment of quality

A quality assessment tool for diagnostic accuracy studies (QUADAS-2) was applied for all included studies to quantify quality [21]. It consists of four key domains: patient selection, index test, reference standard and flow and timing. Risk of bias and concerns regarding applicability (only for the first three domains) were assessed for each domain for every study.

Results

The primary search identified 1.484 articles. Eleven additional articles were found through other sources. After fulfilling inclusion and exclusion criteria and excluding duplicates, 149 studies remained and were included in the review (Fig. 1).

Technical parameters

All studies assessed structural joint damage in gray scale. The overwhelming studies utilized high frequency, linear transducers (range 5-22 MHz). No frequency was provided in 36/149 (24.2%) studies. Other parameters for gray scale such as gain, dynamic range, number of foci, were not standardized or provided in the studies. Two studies [12] focusing on cartilage damage utilized stringent methodology corresponding to a critical review which suggested ensuring an insonation angle of 90 degrees and including the cartilage interface sign when measuring cartilage thickness [22].

Assessed sites

The majority of the included studies assessed any joints of the hands (wrists, metacarpophalangeal, proximal interphalangeal or distal interphalangeal joints) and/or metatarsophalangeal joints (MTPs) (111/149, 74.5%). In 36/149 (24.2%) studies, other joints including the shoulders, knees, hips, sternoclavicular and temporomandibular joints were examined. Fifteen out of 149 studies (10.1%) assessed any joints of the hands and MTPs as well as other joints. All, but 22/149 (14.8%) studies assessed joints bilaterally: 12/149 (8.1%) studies [23–32] scored the clinically more affected side only. The dominant hand and the right hand were assessed in 8/149 (5.4%) [33–40] and 1/149 (0.7%) [41] studies, respectively. One study did not provide information regarding the assessed side [42] (Table 1).

Assessed lesions

Bone erosions

In total, 139/149 (93.3%) included studies assessed erosions in RA patients. Among these, 107/139 (77%) studies used a binary grading (presence/ absence per patient or per joint) method. In 18/139 (12.9%) studies [16,17,25,28,30,32,34,36,41,43–51], a global erosion score was provided, calculated either as the sum of joints with at least one erosion or as the sum of joint quadrants with at least one erosion. In 44/139 (31.7%) studies, a semiquantitative score was calculated including the number and/or size of erosions. Four studies assessed erosions quantitatively by measuring the longitudinal diameter or the size of the erosions in mm [52] and/ or qualitatively (shape, well-defined border, location, presence of overhanging margin)(45, 53) (Table 1).

In the majority of studies (47/139, 33.8%) erosions were assessed according to the OMERACT definition [54] published by Wakefield et al. in 2005: “intraarticular discontinuity of the bone surface that is visible in 2 perpendicular planes”. A similar definition published by Szkudlarek et al. in 2003 [55] was used in 13/139 (9.4%) included studies with “cortical break seen in two perpendicular planes”. No definition at all was provided in 46/139 (33.1%) studies. Four studies (2.9%) included size in the definition of a definitive erosion: $>$ 1mm in 2 studies [56,57], $<$2mm in one study [58] and $>$2 mm in another study [43].

In 105/139 (75.5%) studies, any joints of the hand or the MTPs were assessed for erosions. In 27/139 (19.4%) studies, other joints including shoulder, knee, elbow, talonavicular joint, subtalar joint, hip, sternoclavicular joint and temporomandibular joint were

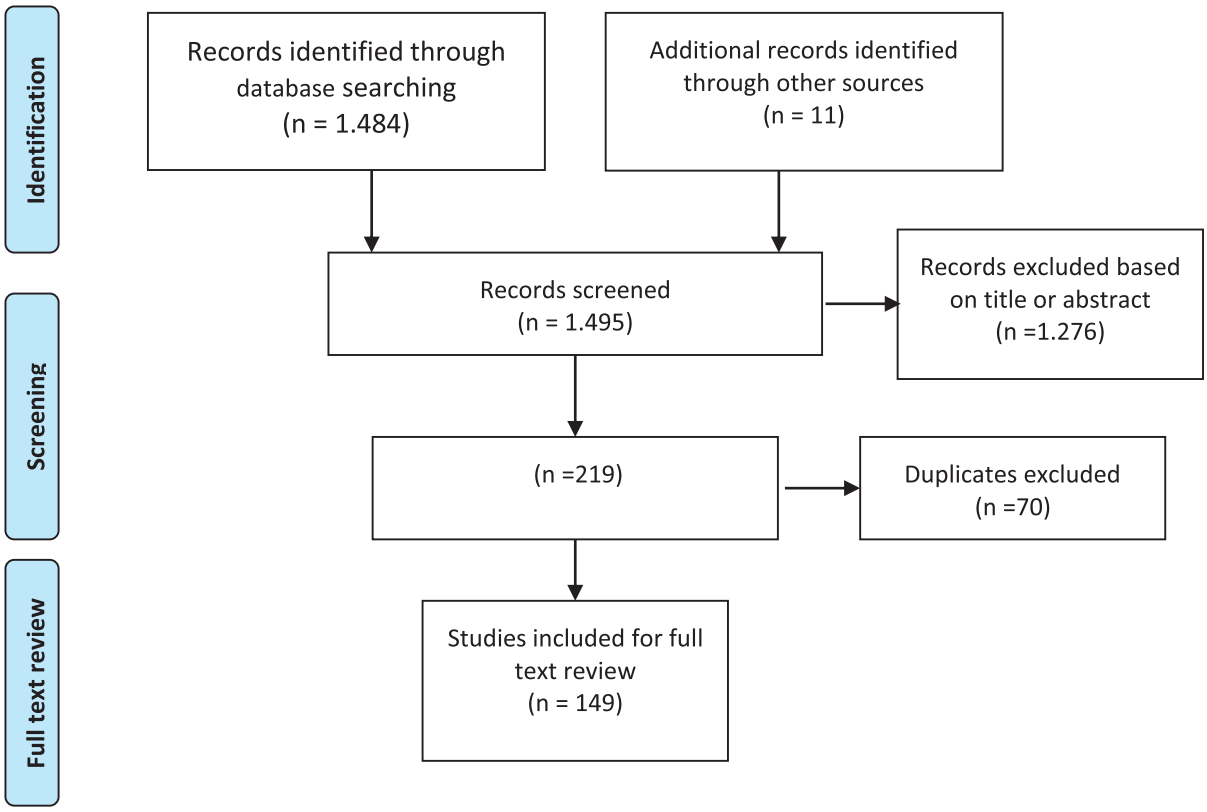

Fig. 1. Flowchart of study selection.

assessed. In 15/139 (10.8%) studies both joints of the hand or MTPs as well as other joints were assessed (Table 1).

Criterion validity assessed as comparison with other imaging methods was investigated in only 20/139 (14.4%) studies [14,23,30,37,39,50,52,59–70], while 27/120 (22.6%) of the remaining studies listed the frequency of detected erosions by ultrasound compared to MRI or CR. Validity was good to excellent (intraclass correlation coefficient (ICC) ≥0.61, kappa (K) ≥ 0.61, agreement ≥ 61% or Kendall's W ≥ 0.61) in 6/14 (42.9%) studies using a binary rating (range: sensitivity: 27-100%, correlation coefficient R (R): 0.3-0.7, K: 0.5-0.9) while 2 studies did not state the exact results. Among studies using semiquantitative scoring, validity was good to excellent in 3/4 (75%) studies (range: agreement: 65-93%, R: 0.3-0.7, Pearson's r=0.68). Inter- or intrarater reliability was assessed in 25/104 (24%) studies. Good to excellent agreement was found in 20/25 studies reporting reliability (80%). Reliability was good to excellent in 14/16 (87.5%) studies using a binary scoring (range: ICC: 0.93-0.99, K: 0.4-0.89, agreement: 88-98%, Kendall's W: 0.85, Pearson's correlation coefficient: 0.9, Gwet's AC1: 0.80), in 10/13 (76.9%) studies using semiquantitative scoring (range: ICC: 0.2-0.97, K: 0.5-1, agreement: 85-98%, R: 0.5-0.8), in 0/2 (0%) studies using a quantitative scoring (range: concordance correlation coefficient:0.5-1, ICC:0.1-0.4) and in 1/1 (100%) study using a qualitative scoring (K=0.8). Progression of erosions, defined as an increase in the number of erosions or semiquantitative score, was assessed in 16/139 (11.5%) studies [25,32,34,35,37,41,43,60,71–78], 9 (56.3%) of which showed a significant difference over time [35,37,41,43,72–74,76,78]. Sensitivity to change was found in 6/13 (46.2%) studies using a binary rating and in 3/4 (75%) using a semiquantitative rating. Feasibility was assessed in only two studies [53,79] in which ultrasound was shown to be feasible when scanning for bone erosions was restricted to few target areas (Table 2).

Enthesophytes and osteophytes

Eight out of 149 (5.4%) studies assessed enthesophytes in RA patients [65,69,80–85]. Results were reported as binary (present/absent). Enthesophytes were assessed according to the OMERACT definition published by Terslev et al. [86] in one study. In two studies (25%) [69,85], enthesophytes were defined as "step-up of bony prominence, seen in two perpendicular planes at the end of the bone contour of the enthesis". Interobserver agreement was reported as good (K=0.68) in a single study, while criterion validity was rated as excellent (ultrasound vs. CR; K=0.86) in an additional study [65,83]. A single study assessed insertions of the 2nd to 4th flexor tendons of the hand, while the other studies examined entheses of other joints/sites including the knee, heel, shoulder and midfoot joints (Tables 1 and 2).

Osteophytes were assessed in 15/149 (10.1%) studies [56,57,69,80,85,87–96] all of which used binary grading. One study [93] additionally assessed osteophytes quantitatively by measuring the longitudinal length. Osteophytes were defined as bony prominence or enlargement in 6/15 (40%) studies [56,57,69,85,89,91] and as irregularity of the bone contour in one study (10%) [87] while no definition was given in the remaining 8/15 (53.3%) studies. Three studies found good to excellent interobserver reliability of osteophytes (K=0.64-0.88) [89]. Seven out of 15 (46.7%) studies assessed the joints of the hand. Other studies assessed the sternoclavicular joint, the hip, the knee, the ankle and the shoulder (Tables 1 and 2).

Cartilage damage

Among the 149 included studies, cartilage damage was assessed in 24 (16.1%) studies. Four out of the 24 included studies (16.7%) assessing cartilage used the semiquantitative score proposed by Disler et al. [77,97–99]. In the remaining studies, cartilage damage (binary/semiquantitative) was defined by partial or full thickness defects of the cartilage layer in 7/24 (29.2%) studies

Table 1
Overview of included studies.

Ref.	Population	Technique	No. patients	Joints assessed	Scoring system(s)	Lesions assessed
[59]	RA/HC	CR/US/MRI	65	Shoulder	B	BE
[34]	RA/PsA	US/CR	120	MCP2,3/PIP2,3/MTP2,5	B/ESS	BE
[43]	RA	US/CR	21	MCP2,5/MTP5/most swollen PIP	B/ESS	BE
[60]	RA	US/MR/CR/CT	49	Wrist/MCP1–5	B	BE
[61]	RA	US/CT	49	MCP2-5	B/S	BE
[117]	Susp. RA	US/CR	58	[$]	B	BE
[118]	RA	US	20	PIP2/MCP2-3/MTP5	B/S	BE
[35]	EA	CR/US/MRI	70	Distal ulna	S	BE
[119]	RA	US	48	MTP5	B	BE
[71]	RA	US/CR	82	Elbow/wrist/MCP2-3/ knee/ankle	B	BE
[17]	RA	US/CR	24	MCP1-5	B/ESS	BE
[23]	RA	US/CR	38	Wrist/MCP1-5/PIP1-5/MTP 2-5	S	BE
[72]	RA	US	40	1 PIP/1 MCP	S	BE
[62]	RA	US/MRI	30	MCP2-5/PIP2-5	B	BE
[66]	RA	US	30	MCP2-3/PIP2/MTP1-2	S	BE
[63]	RA/HC	US/MR/CR	60	MCP2-5/PIP2-5	B	BE
[18]	RA/HC	US/MRI/CR	60	MTP1-5	B/S	BE
[33]	RA	US/CR/MRI	100	MCP1-5	B/S/Q	BE
[120]	RA/PsA/Go/OA/HC	US	310	Distal radius and ulna/MCP2- 3,5/PIP 2-3/MTP1+5	B/S	BE
[73]	EA	US	63	Wrist/MCP2+5/MTP5	B/S	BE
[64]	RA	US/MRI	50	Wrist/MCP2-5	B	BE
[74]	EA	US/CR	79	Hand and feet	B	BE
[41]	RA	US/CR/MRI	46	Wrist/MCP1-5/PIP1-5	B/ESS	BE
[24]	RA	US/CR/MRI	26	MCP1-5/MTP1-5	B	BE
[45]	RA/Go	US/CR	80	MTP1-5	B/ESS/QI/Q	BE
[75]	RA,	US	274	MCP2-3+5/MTP5	B	BE
[50]	RA	US/CR	122	MCP2-3+5/MTP2-3+5	S/ESS	BE
[16]	RA	US	77	MCP1-5/PIP1-5/MTP1-5	S/ESS	BE
[37]	RA/AS/CTD/UA	US/CR/MRI/SZ	49	MCP1-5/PIP1-5/DIP1-5	B	BE
[121]	RA	US	32	MTP2+5	B	BE
[25]	RA	3DUS	26	MCP2+5/MTP1+5	B/ESS	BE
[76]	RA	2D/3DUS	85	MCP1-5	B	BE
[39]	ERA	3DUS/CT/CR	20	Wrist/MCP2-5/PIP2-5	B	BE
[30]	RA	US/MRI	31	Wrist/MCP2-4/PIP2-4	B/ESS	BE
[52]	RA	3DUS/MRI	28	MCP2-3	B/S/Q	BE
[32]	RA/PsA/AS	US	45	Wrist/MCP2-3/PIP2-3/MTP2+5	B/ESS	BE
[67]	RA/HC	US/HR-pQCT	81	MCP1-5/PIP1-5	B/Q	BE
[68]	RA	US/CR	108	MCP2-3+5/MTP2-3+5	S	BE
[122]	RA	US/CR	108	MCP2-3+5/MTP2-3+5	B/S	BE
[78]	RA	US/CR	60	WRIST/MCP1-5	B	BE
[70]	ERA	US/MRI	39	MTP2-5	B	BE
[83]	RA/PsA/HC	US	94	Flexor tendons	B	EP
[89]	RA/HC	US	206	STCJ	B	BE, OP
[65]	RA/PsA/OA	US/CR	598	Heel	B	BE, EP
[69]	RA	US/MRI	35	Heel, ankle	B	BE, OP, EP
[85]	RA/HC	US	70	Heel, ankle	B	BE, OP, EP
[12]	RA/HC/cadaveric specimen	US/CR	47	MCP	Q/summary score	CTh
[104]	RA	US	20	MCP2+3	B, S	CD
[27]	RA	US/MRI	30	Knee	B,/Q	CD, CTh
[111]	RA	US	60	Wrist/MCP2-3/PIP2-3	B,/S	BE, CD
[14]	RA	US/CR	125	Elbow	S	BE, CD
[15]	RA	US/CR	425	Tender and/or swollen joints: MCP/PIP/wrist/ elbow	S	BE, CD
[105]	RA/HC	US	39	Wrist/MCP1-5	S	BE, CD
[101]	ERA	US/CR	48	Wrist/MCP2-3/PIP2-3	B,/S	BE, CD
[77]	RA	US/CR	132	MCP1-5	S	BE, CD
[99]	RA/OA	US	86	MCP2-5	B,/S	CD
[103]	RA/HC	US/CR	145	MCP2-5/PIP2-5	S,/Q	CD
[46]	RA	2D/3DUS	31	Wrist/MCP2-3/PIP2-3/MTP2,5	B/ESS	BE
[123]	ERA/RA/H/RMD	US/CR	198	Wrist/MCP1-5/PIP1-5/DIP1-5	B	BE
[124]	ERA	US	34	Wrist/MCP2-5/PIP1-5	S	BE
[125]	RA	US	60	Wrist/MCP 1-5/PIP 1-5	B	BE
[126]	RA	US/CEUS	39	Wrist/MCP1-5/PIP1-5/elbow/knee	S	BE
[127]	RA	US	41	Wrists/MCP 1-5/PIP1-5	B	BE
[128]	RA/HC	US	83	Ankle	B	BE
[129]	EA	CR/US	126	MCP2+5/MTP5	B/S	BE
[130]	RA	CR/US/MRI	43	Shoulder	S	BE
[131]	RA	US	25	Wrist/MCP2+5/PIP3/knee	S	BE
[132]	RA	US	30	MCP1-5/PIP1-5	B	BE
[133]	RA/HC	US	138	[#]	B/S	BE
[134]	RA/HC	US	89	Shoulder	B	BE

(*continued*)

Table 1 (*Continued*)

Ref.	Population	Technique	No. patients	Joints assessed	Scoring system(s)	Lesions assessed
[135]	RA	US	24	MCP2-5	B/S/Q	BE
[136]	RA	US/CR	47	Wrist/MCP1-5/PIP 2-5	B	BE
[137]	EA	US/MRI	62	Wrist/MCP1-5/PIP1-5	S	BE
[138]	RA	US	22	MCP2-3/PIP2-3/MTP2-5	B	BE
[139]	EA/HC	US	84	Wrists/MCP 2-5	B	BE
[47]	EA	US/CR	40	MCP1-5	B/ESS	BE
[140]	EA	US	174	Hand and finger joints/MTP1-5	B	BE
[36]	RA	US	30	Wrist/MCP2-3/PIP2-3/MTP2+5	ESS	BE
[141]	EA	US	40	MCP2+5	B	BE
[142]	RA	US	51	@	B	BE
[143]	EA	CR/US	30	MTP5	B/S	BE
[144]	RA	US/CR	122	MCP2-3+5/MTP2-3+5	S	BE
[53]	ERA/RA	US	110	MCP2+5/ulnar head/MTP1+5	B/Q	BE
[145]	IA	US/CR	144	Wrist/MCP 2-5/MTP5/most swollen PIP	B	BE
[38]	IA	US/MRI	32	Wrist/MCP1-5	B	BE
[28]	RA	US	432	Wrist/MCP2-3/PIP2-3/MTP2+5	B/ESS	BE
[146]	RA	US/CR/MRI/CT	26	shoulder	B/S	BE
[29]	RA	US	20	Wrist/MCP2+3/PIP 2+3/MTP2+5	B	BE
[147]	RA	US	40	Wrist/MCP1-5/PIP1-5	B	BE
[148]	Susp RA	US/CR	94	Wrist/MCP1-5/PIP1-5	B	BE
[149]	ERA	US/MRI	39	Wrist/MCP1-5/PIP1-5	B	BE
[150]	RA	US/CR	288	Wrist/MCP1-5/PIP1-5/elbow/shoulder/knee	B	BE
[31]	RA/AS/HC	US	114	Shoulder	B	BE
[151]	RA	US/MRI	30	Wrist/MCP2-4	B	BE
[152]	RA/OA/HC	US	156	MTP1-5	B	BE
[48]	RA	US/CR	30	MTP1-5/ tibiotalar joint, subtalar joint, talonavicular joint	B/ESS	BE
[49]	EA	US/MRI/CR	30	Wrist/MCP2-5	S/ESS	BE
[40]	RA	US	20	Wrist/MCP2-5/PIP2-5/MTP2-5	B/S	BE
[44]	EA	US/CR	127	MCP2+5/MTP5	B/ESS/S	BE
[153]	RA	US/CR	40	n/a	B	BE
[154]	RA/HC	US	120	Sternoclavucular joint	B	BE
[155]	RA/RMD	US	101	Wrist /MCP1-5/PIP1-5/MTP1-5	B	BE
[156]	RA	US	90	10 hand joints	B	BE
[157]	RA/HC	US	180	Wrist /MCP2-3/PIP2-3	B	BE
[158]	UA	US	204	Wrist /MCP2-3/PIP2-3/MTP2+5	B	BE
[159]	RA	US	50	Wrist/MCP2-5/PIP2-5	B	BE
[160]	RA/HC	US	80	Wrist/MCP2-3/PIP2-3/MTP2+5	B/S	BE
[161]	RA	US	62	Wrist/MCP2-3/PIP 2-3/MTP2+5	B	BE
[162]	RA	US	86	Wrist	B	BE
[163]	RA	US/CR	50	Wrist/MCP1-5/PIP1-5	S	BE
[79]	RA	US	30	Elbow/Wrist/MCP1-5/PIP1-5, ankle, MTP1-5	B	BE
[164]	RA	US	30	n/a	B	BE
[51]	RA	US	30	Elbow/Wrist/MCP1-5/PIP1-5, ankle, MTP1-5	B,/ESS	BE
[165]	RA	US	30	Elbow/Wrist/MCP1-5/PIP1-5, ankle, MTP1-5	B	BE
[166]	RA	US	30	Elbow/Wrist/MCP1-5/PIP1-5, ankle, MTP1-5	B	BE
[42]	RA	US	62	n/a	B	BE
[167]	RA/ACPA HC	US/CR	82	Joints of the hand and feet	B	BE
[168]	RA	US, MRI	80	MCP2-5/PIP2-5	B	BE
[169]	ACPA HC/ ACPA arthritis	US	400	MCP2+5/MTP5	B/ S	BE
[170]	RA	US	30	Elbow/Wrist/MCP1-5/PIP1-5, ankle, MTP1-5	B	BE
[171]	ACPA HC/ ACPA arthritis	US	64	Wrist/MCP1-5/ PIP1-5/DIP1-5/Joints of the feet	B	BE
[172]	RA	US	30	Wrist/MCP1-5/PIP1-5/MTP1-5/elbow/ankle	B	BE
[88]	ERA	US	98	22 joints of the hand	B	BE, OP
[82]	RA/AS/HC	US	62	*	B	BE, EP
[84]	RA/PsA	US	80	Knee	B	BE, EP
[57]	RA/OA/HC	US	50	MCP1-5/PIP1-5	B	BE, OP
[90]	RA	US	37	Shoulder	B/S	BE, OP
[80]	RA	US	100	Shoulder	B	BE, EP, OP
[56]	RA/OA/HC	US	52	MCP1-5/PIP1-5	B/S	BE, OP
[81]	RA	US	100	MTP1-5/PIP1-5/midfoot joints	B	BE, EP
[91]	RA	US	46	Wrist/MCP1-5/PIP1-5	B	BE, OP
[92]	RA	US	224	Wrist/MCP1-5/PIP1-5	B	BE, OP
[94]	RA/HC	US	44	SCJ/manubriosternal joint	B	BE, OP, ankylosis
[95]	RA	US	43	Wrist/MCP1-5/PIP1-5/elbow/shoulder/knee	B	BE, OP
[96]	RA/OA/HC	US	120	Wrist/MCP1-5/PIP1-5/DIP1-5	B	BE, OP
[108]	RA, HC	US	80	Knee	Q	CTh
[107]	RA/OA/HC	US	138	Knee	B,/Q	CD, CTh
[109]	RA	US	100	Knee	B	CD, BE
[26]	RA/DSD	US	178	Shoulder	B	BE, CD
[106]	RA	US	20	MCP1-5/ hand tendons	B	BE, CD
[100]	RA	US/MRI	50	Wrist/MCP2-5	S	BE, CD
[93]	RA/OA	US	42	Knee	B	BE, CTh, OP
[87]	RA	US	52	Hip	B	BE, CD, OP
[110]	RA	US	61	Knee	Q	CTh

(*continued*)

Table 1 (*Continued*)

Ref.	Population	Technique	No. patients	Joints assessed	Scoring system(s)	Lesions assessed
[112]	RA	US	60	Wrist/MCP1-5	S	BE, CD
[116]	RA	US/CR/MRI	20	TMJ	B/S	BE, DDP
[113]	RA	US	100	Wrist/MCP1-5/PIP1-5	B,/S	BE, CD
[102]	RA/HC	US	40	MCP2-5	S/Q	CD, CTh
[114]	RA	US	53	Wrist/MCP1-5/PIP1-5	B	BE, CD

[$]MCP1-5, PIP1-5, MTP2-5, elbow, wrist, shoulder, knee, ankle.
[#]PIP 2,3; MCP 2,3; MTP 1, 2, 5, wrist, elbow, shoulder, hip, knee, ankle, talonavicular joint, subtalar joint.
[@]Achilles tendon, plantar fascia, quadriceps tendon insertion on patella, patellar tendon insertion on the distal pole of the patella, tibialis anterior tendon, triceps tendon, common flexor and extensor tendons.
[*]Patella, patellar tendon insertion at the tibial tuberosity, Achilles tendon, plantar aponeurosis, supraspinatus tendon, biceps brachii tendon
AC, accuracy; AG, agreement; AS, axial spondylarthritis; B, binary; BE, bone erosions; CD, cartilage damage; CT, computed tomography; CTD, connective tissue disease; CTh, cartilage thickness; CR, conventional radiograph; EA, early arthritis; EP, enthesophyte; ERA, early rheumatoid arthritis; ESS, erosion summary score; Go, gout; HC, healthy control; HR-pQCT, high-resolution peripheral quantitative computed tomography; MCP, metacarpophalangeal joint; MRI, magnetic resonance imaging; MTP, metatarsophalangeal joint; OA, osteoarthritis; PIP, proximal interphalangeal joint; PsA, psoriatic arthritis; Q, quantitative; RA, rheumatoid arthritis; S, semiquantitative; STCJ, sternoclavicular joint; SZ, bone scintigraphy; TMJ, temporomandibular joint; UA, undifferentiated arthritis; US, ultrasound.

Table 2
Overview of included studies and reliability, validity, feasibility or sensitivity to change.

Ref.	Reliability		Validity	Feasibility	STC
	Intrarater	Interrater			
[59]	n/a	n/a	SE: 85.4%	n/a	n/a
[34]	K: 0.64	K: 0.56	n/a	n/a	N
[43]	n/a	K: 0.98	n/a	n/a	Y
[60]	ICC: 0.93	n/a	SE: 44%/ SP: 95%/ ACC:84%	n/a	N
[61]	n/a	n/a	SE: 44%/ SP: 95%/ ACC:84%	n/a	n/a
[117]	K: 0.93	n/a	n/a	n/a	n/a
[118]	n/a	K: 0.4-0.99	n/a	n/a	n/a
[35]	n/a	n/a	n/a	n/a	Y
[119]	n/a	K: 0.8	n/a	n/a	n/a
[71]	n/a	n/a	n/a	n/a	N
[17]	n/a	K: 0.74	n/a	n/a	n/a
[23]	n/a	n/a	R: 0.41-0.81	n/a	n/a
[72]	n/a	n/a	n/a	n/a	Y
[62]	n/a	n/a	K: 0.55	n/a	n/a
[66]	n/a	K: 0.68	n/a	n/a	n/a
[63]	n/a	n/a	AC: 0.96/ SE:0.59/ SP: 0.98	n/a	n/a
[18]	n/a	n/a	SE: 0.79/ SP: 0.97/ AC: 0.96	n/a	n/a
[33]	K: 0.75	K: 0.76	n/a	n/a	n/a
[120]	K: 0.82-0.87	n/a	n/a	n/a	n/a
[73]	n/a	n/a	n/a	n/a	Y
[64]	n/a	n/a	K: 0.48	n/a	n/a
[74]	n/a	n/a	n/a	n/a	Y
[41]	n/a	n/a	n/a	n/a	Y
[24]	n/a	K: 0.81	n/a	n/a	n/a
[45]	n/a	K: 0.81	n/a	n/a	n/a
[75]	n/a	n/a	n/a	n/a	N
[50]	ICC: 0.96	ICC: 0.97	AG: 0.93	n/a	n/a
[16]	n/a	K: 0.72	n/a	n/a	n/a
[37]	n/a	n/a	SE	n/a	Y
[121]	n/a	K: 0.64	n/a	n/a	n/a
[25]	ICC: 0.99	n/a	n/a	n/a	N
[76]	n/a	n/a	n/a	n/a	Y
[39]	n/a	KW: 0.85	SE: 0.9/ SP: 0.55	n/a	n/a
[30]	n/a	K: 0.59	SE: 0.27-1/ SP: 0.47-0.75	n/a	n/a
[52]	ICC: 0.13-0.86	n/a	R: 0.26-0.75	n/a	n/a
[32]	n/a	n/a	n/a	n/a	N
[67]	P>0.9	n/a	SP: 0.97-1/ SE: 0.4-0.5	n/a	n/a
[68]	n/a	n/a	P: 0.68	n/a	n/a
[122]	ICC: 0.96/ G: 0.81	ICC: 0.97	n/a	n/a	n/a
[78]	n/a	n/a	n/a	n/a	Y
[70]	n/a	n/a	K: 0.01	n/a	n/a
[83]	n/a	K: 0.69	n/a	n/a	n/a
[89]	n/a	K: BE: 0.7/ OP: 0.65	n/a	n/a	n/a
[65]	n/a	n/a	K: BE: 0.86/ EP: 0.83-0.89	n/a	n/a
[69]	n/a	K: BE: 0.65-0.89/ OP: 0.64-0.83	K: BE: 0.06/ OP: K: 0.26	n/a	n/a
[85]	n/a	K: 0.71–0.88	n/a	n/a	n/a
[12]	ICC: 0.8	ICC: 0.8	ICC: 0.61	n/a	n/a
[104]	n/a	K: 0.36- 0.83	n/a	n/a	n/a
[27]	n/a	n/a	K: 0.66-0.85	n/a	n/a
[111]	n/a	K: BE: 0.7-1/ CD: 0.3-0.6	n/a	n/a	n/a
[14]	AG: 0.91	AG: 0.89	AG: 0.65	n/a	n/a

(*continued*)

Table 2 (*Continued*)

Ref.	Reliability		Validity	Feasibility	STC
[15]	AG: 0.91	AG: 0.89	n/a	n/a	n/a
[105]	n/a	ICC: 0.11-1	n/a	n/a	n/a
[101]	n/a	K: BE: 0.42-0.47/ CD: 0.8	n/a	n/a	n/a
[77]	n/a	n/a	n/a	n/a	N
[99]	n/a	n/a	K: 0.63	n/a	n/a
[103]	Kr: 0.81	Kr: 0.6	Rho: 0.66	n/a	n/a
[46]	n/a	n/a	n/a	n/a	n/a
[123]	n/a	n/a	n/a	n/a	n/a
[124]	n/a	n/a	n/a	n/a	n/a
[125]	n/a	n/a	n/a	n/a	n/a
[126]	n/a	n/a	n/a	n/a	n/a
[127]	n/a	n/a	n/a	n/a	n/a
[128]	n/a	n/a	n/a	n/a	n/a
[129]	n/a	n/a	n/a	n/a	n/a
[130]	n/a	n/a	n/a	n/a	n/a
[131]	n/a	n/a	n/a	n/a	n/a
[132]	n/a	n/a	n/a	n/a	n/a
[133]	n/a	n/a	n/a	n/a	n/a
[134]	n/a	n/a	n/a	n/a	n/a
[135]	n/a	n/a	n/a	n/a	n/a
[136]	n/a	n/a	n/a	n/a	n/a
[137]	n/a	n/a	n/a	n/a	n/a
[138]	n/a	n/a	n/a	n/a	n/a
[139]	n/a	n/a	n/a	n/a	n/a
[47]	n/a	n/a	n/a	n/a	n/a
[140]	n/a	n/a	n/a	n/a	n/a
[36]	n/a	n/a	n/a	n/a	n/a
[141]	n/a	n/a	n/a	n/a	n/a
[142]	n/a	n/a	n/a	n/a	n/a
[143]	n/a	n/a	n/a	n/a	n/a
[144]	n/a	n/a	n/a	n/a	n/a
[53]	n/a	n/a	n/a	Y	n/a
[145]	n/a	n/a	n/a	n/a	n/a
[38]	n/a	n/a	n/a	n/a	n/a
[28]	n/a	n/a	n/a	n/a	n/a
[146]	n/a	n/a	n/a	n/a	n/a
[29]	n/a	n/a	n/a	n/a	n/a
[147]	n/a	n/a	n/a	n/a	n/a
[148]	n/a	n/a	n/a	n/a	n/a
[149]	n/a	n/a	n/a	n/a	n/a
[150]	n/a	n/a	n/a	n/a	n/a
[31]	n/a	n/a	n/a	n/a	n/a
[151]	n/a	n/a	n/a	n/a	n/a
[152]	n/a	n/a	n/a	n/a	n/a
[48]	n/a	n/a	n/a	n/a	n/a
[49]	n/a	n/a	n/a	n/a	n/a
[40]	n/a	n/a	n/a	n/a	n/a
[44]	n/a	n/a	n/a	n/a	n/a
[153]	n/a	n/a	n/a	n/a	n/a
[154]	n/a	n/a	n/a	n/a	n/a
[155]	n/a	n/a	n/a	n/a	n/a
[156]	n/a	n/a	n/a	n/a	n/a
[157]	n/a	n/a	n/a	n/a	n/a
[158]	n/a	n/a	n/a	n/a	n/a
[159]	n/a	n/a	n/a	n/a	n/a
[160]	n/a	n/a	n/a	n/a	n/a
[161]	n/a	n/a	n/a	n/a	n/a
[162]	n/a	n/a	n/a	n/a	n/a
[163]	n/a	n/a	n/a	n/a	n/a
[79]	n/a	n/a	n/a	n/a	n/a
[164]	n/a	n/a	n/a	n/a	n/a
[51]	n/a	n/a	n/a	n/a	n/a
[165]	n/a	n/a	n/a	n/a	n/a
[166]	n/a	n/a	n/a	n/a	n/a
[42]	n/a	n/a	n/a	Y	n/a
[167]	n/a	n/a	n/a	n/a	n/a
[168]	n/a	n/a	n/a	n/a	n/a
[169]	n/a	n/a	n/a	n/a	n/a
[170]	n/a	n/a	n/a	n/a	n/a
[171]	n/a	n/a	n/a	n/a	n/a
[172]	n/a	n/a	n/a	n/a	n/a
[88]	n/a	n/a	n/a	n/a	n/a
[82]	n/a	n/a	n/a	n/a	n/a
[84]	n/a	n/a	n/a	n/a	n/a
[57]	n/a	n/a	n/a	n/a	n/a

(*continued*)

Table 2 (*Continued*)

Ref.	Reliability		Validity	Feasibility	STC
[90])	n/a	n/a	n/a	n/a	n/a
[80]	n/a	n/a	n/a	n/a	n/a
[56]	n/a	n/a	n/a	n/a	n/a
[81]	n/a	n/a	n/a	n/a	n/a
[91]	n/a	n/a	n/a	n/a	n/a
[92]	n/a	n/a	n/a	n/a	n/a
[94]	n/a	n/a	n/a	n/a	n/a
[95]	n/a	n/a	n/a	n/a	n/a
[96]	n/a	n/a	n/a	n/a	n/a
[108]	n/a	n/a	n/a	n/a	n/a
[107]	n/a	n/a	n/a	n/a	n/a
[109]	n/a	n/a	n/a	n/a	n/a
[26]	n/a	n/a	n/a	n/a	n/a
[106]	n/a	n/a	n/a	n/a	n/a
[100]	n/a	n/a	n/a	n/a	n/a
[93]	n/a	n/a	n/a	n/a	n/a
[87]	n/a	n/a	n/a	n/a	n/a
[110]	n/a	n/a	n/a	n/a	n/a
[112]	n/a	n/a	n/a	n/a	n/a
[116]	n/a	n/a	n/a	n/a	n/a
[113]	n/a	n/a	n/a	n/a	n/a
[102]	n/a	n/a	n/a	n/a	n/a
[114]	n/a	n/a	n/a	n/a	n/a

AC, accuracy; AG, agreement; G, Gwet's AC1; ICC, intraclass correlation; K, kappa; Kr, Krippendorff's alpha; KW, Kendall's W coefficient; N, no; n/a, not available; P, Pearson's correlation; SE, sensitivity; SP, specificity; STC, sensitivity to change; Y, yes.

[14,15,26,100–103] or by cartilage irregularity mainly of the margins in 3/24 (12.5%) studies [87,104,105] or general irregularity of the cartilage in 3/24 (12.5%) studies [27,106,107]. Nine out of the 24 studies (37.5%) only or additionally assessed cartilage thickness quantitatively [12,27,93,102,103,107–110] (Table 1).

Joints of the hands were assessed in 15 studies [12,15,77,99-106,111–114] while 9 studies [14,26,27,87,93,107,108,110,115] assessed other joints including the knee, shoulder, elbow and hip joints. Cartilage damage was rated as binary (cartilage present/absent per joint or per joint quadrant) in 12 studies [14,15,77,99–105,112,113], quantitatively by measuring cartilage thickness in 8 studies [12,27,102,103,107–110] and/or semiquantitavely in 12 studies [14,15,77,99–105,112,113]. Among the studies, which utilized a semiquantitative scoring system, 2 used a damage score combining bone erosions and cartilage loss [14,15] (Table 1).

Interobserver reliability and criterion validity expressed as comparison with other imaging methods were analyzed in 8/24 (33.3%) [12,14,15,101,103–105,111] and 5/24 (20.8%) studies [12,15,27,99,103], respectively. Five of 8 (62.5%) studies reported good to excellent agreement, including the two using the combined bone erosions and cartilage loss score [14,15]. Agreement was rated good to excellent in 1/2 (50%) studies using a binary rating (range of K: 0.6-0.7), in 3/6 (50%) studies using a semiquantitative rating (range of ICC: 0.1-1, of K: 0.3-0.8, of AG: 89-91%) and in 2/2 (100%) studies using a quantitative rating (ICC: 0.8, Krippendorff's alpha 0.6-0.81). Criterion validity was reported to be good to excellent in 1/1 (100%) study using binary scoring (K=0.7-0.9), in 3/3 (100%) studies using a semiquantitative scoring (AG: 65%, K: 0.63, rho: 0.66) and in 1/2 (50%) study using a quantitative scoring (ICC: 0.6%, rho: -0.57). One (100%) study assessing cartilage damage semiquantitatively reported no progression of cartilage damage [77]. Condylar cartilage was found to be thicker when measured by ultrasound as compared to MRI (2.1mm vs. 1.85mm, $p<0.001$) [27] (Table 2).

Malalignment and ankylosis

Only a single study assessed malalignment by ultrasound [116], defined as the displacement of the temporomandibular joint disc indirectly according to the anterior capsule–condyle distances. Malalignment was scored in binary fashion (Table 1).

One study assessed ankylosis of the sternoclavicular and the manubriosternal joints [94]. Authors rated ankylosis as present or absent (binary) without providing a definition (Table 1).

Quality assessment

All 149 studies included in the full text review underwent scoring by QUADAS-2. In each assessed term, less than 55% revealed concerns regarding applicability or bias among studies where the addressed domain was applicable. The biggest risk of bias was expressed in "flow and timing", were 53% of the studies where this was applicable were found to have such a risk (Fig. 2).

Discussion

One of the major advantages of ultrasound is its capability to visualize and quantify synovitis, which is predictive of structural damage. However, in contrast to the utility of ultrasound in evaluating inflammatory activity expressed by synovitis, much less has been published regarding the sonographic assessment of structural damage in RA. This SLR conducted according to the OMERACT filter 2.1, aimed to summarize all available data specifically on this latter topic.

Most included studies assessed bone erosions. A well-conducted systematic literature by the OMERACT Ultrasound WG published in 2016 included studies on erosions assessed by ultrasound until May 2014 [3]. Our review updates this previous study up to October 2020 and, in order to provide a more complete picture, also covers other elementary forms of structural damage seen in RA.

Although CR is currently used to detect erosions, ultrasound was more sensitive than CR in all studies comparing the prevalence of erosions measured by ultrasound and CR. MRI was even more sensitive than ultrasound. One possible reason for the higher sensitivity of MRI lies in the fact that it is capable of visualizing the entire joint while ultrasound only sees facets with an acoustic window. With the majority of studies utilizing MRI as the reference method, ultrasound showed a mostly good to excellent criterion validity and interobserver agreement. Furthermore, sensitivity to change was reported in the majority of studies suggesting ultrasound to be a sensitive outcome measurement tool to assess changes over time. Only five studies compared bone erosions assessed by ultrasound with CT

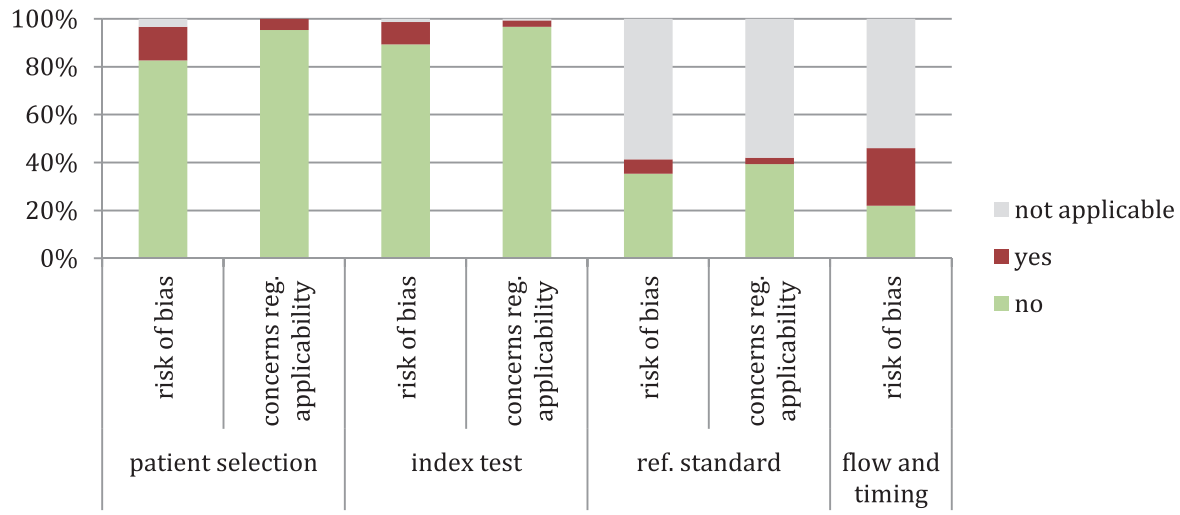

Fig. 2. Results of the quality assessment tool for diagnostic accuracy studies (QUADAS-2) for all studies included in the systematic literature review (n=149); concerns reg applicability: concerns regarding applicability; ref. standard: reference standard.

[39,60,61,67,146]. Three studies [46,60,61] considered CT as the gold standard to calculate sensitivity and specificity of ultrasound to detect erosions. One study compared the frequency of erosions detected by ultrasound and CT [146] and detected more erosions by ultrasound.

Included studies which did not show changes of erosions had follow-up times of 22 weeks [71], 6 months [34,75] and 12 months [25,32,60,77] these time periods however might be too short to detect differences.

Most radiographic scores including erosions use semiquantitative scores [173]. While the majority of the ultrasound studies included in this SLR scored erosions in binary fashion as present or absent on patient or joint level or in each joint quadrant, approximately a third of the studies used a semiquantitative scoring method. This method was based either on the number of erosions per joint or the size of the erosions or by a combination thereof. Counting erosions has the disadvantage that in case two small erosions merge into one big erosion, progression might be scored as improvement. In contrast, additional small erosions may not be taken into account if only the largest erosion is counted. Thus, it seems optimal to consider both size and number of erosions.

Cartilage damage was assessed in 19 studies. It was rated mostly in binary fashion (cartilage damage present/ absent per joint or joint quadrant), quantitatively by measuring cartilage damage or semiquantitatively. One study compared cartilage thickness measured by ultrasound with the actual thickness subsequently measured in cadaveric specimen. Another study measured distal femoral cartilage thickness. Generally, intra- and interobserver reliability was moderate to excellent in the included studies. Compared to measuring the actual cartilage thickness, the binary or semiquantitative score is independent of the patients demographic (age, gender, etc.) and physical (height, weight, etc.) characteristics as healthy cartilage thickness might differ from person to person based on these factors. A recently published semiquantitative ultrasound scoring system for cartilage damage by the OMERACT Ultrasound WG was shown to be reliable in web-based and patient-based exercises and has already been validated in an independent patient cohort [2,147].

Enthesophytes are typical manifestations of psoriatic arthritis and osteoarthritis [174]. Three studies assessed enthesophytes in patients with psoriatic arthritis and those with RA. The studies reported overall good interobserver agreement, although it should be pointed out that enthesophytes were found to be quite rare in RA.

Malalignment or subluxation is widely accepted as clinical feature of structural damage in RA and is part It is part of several radiographic damage scores [175,176]. However, only one included study assessed malalignment by ultrasound, highlighting a need for future studies in this area.

Although theoretically all synovial joints can be affected in RA, screening all joints by ultrasound for damage is not feasible. The detection of damage is important for diagnosis, evaluation of therapy as well as for its predictive value. Target joints for assessment of structural damage should be those that are affected often and early in the course of the disease. Small joints of the hands and feet are affected in the majority of patients with RA and studies showed that they are predictive of composite scores including both small and large joints. Furthermore, MTP joints have been shown to be the site where erosions initially develop [177]. Thus, most CR- based damage scores include hands and feet [173,175–177]. Similarly, most included ultrasound studies assessed joints of the hand and/or MTPs. Only few studies included large joints, which limits the generalizability of this review to all joints. The assessment of small joints of the hands and feet however seems feasible and practical considering they are early and frequent locations for structural damage. RA is a symmetrical disease. All but 22 studies assessed joints bilaterally. In several studies, more erosions with faster progression were found on the dominant hand compared to the non-dominant hand [178,179]. In contrast, synovitis is not thought to develop more often on the dominant hand [180]. Whether assessing structural joint damage by ultrasound on one side only is sufficient, will have to be addressed in future studies. In order to correctly interpret structural damage assessed by ultrasound, the recognition of the frequency and characteristics of these features in healthy individuals is important. Due to the fact that ultrasound seems to be more sensitive than CR, sonographically detected damage should be interpreted with particular caution. Several studies found ultrasound signs of synovitis as well as structural damage in healthy individuals [181–183].

While this review aims to cover the elementary forms of structural damage seen in RA, damage to periarticular and articular soft tissues, such as ligaments, tendons and muscles were not included, which is a limitation. We also did not include joint space narrowing, since this mainly corresponds to cartilage loss and also because ultrasound is not considered to be an ideal modality for its assessment.

In conclusion, the findings of this systemic literature review suggest that ultrasound is a valid and reliable outcome measurement tool to detect joint damage, particularly in small joints of the hands and feet where validated definitions and scoring system exist. Erosions and cartilage damage were the most often assessed and most prevalent features. The development of a composite or combined

ultrasound damage score and the determination of target joints are tasks for future studies. These should ideally consist of consensus definitions and scanning characteristics of elementary lesions of structural damage, the scoring thereof, followed by validation of such lesions and scoring systems, first in web-based and patient-based exercises, and finally in clinical studies.

Declaration of Competing Interest

None

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.tranon.2021.101079.

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